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Comparison of negative pressure wound therapy and moist wound care in patients with diabetic foot ulcers

A protocol for systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: This study conducted a meta-analysis to compare the effectiveness and safety of the negative pressure wound therapy (NPWT) with the moist wound care (MWC) in the treatment of diabetic foot ulcers (DFUs).

Methods: The PubMed, EMBASE, and CENTRAL were searched by 2 of the authors, to identify randomized controlled trials comparing the clinical outcomes of patients treated with NPWT versus MWC for DFUs. Meta-analyses were performed for several outcomes, including wound healing results, amputation or resection incidence, and risk of adverse events, utilizing the "meta" package of R language version 4.0.3.

Results: A total of 10 trials (619 patients in NPWT group and 625 in MWC group) and 8 trials were included for the qualitative and quantitative syntheses, respectively. As a result, significantly lower risk of non-closure of the wound (risk ratio [RR] = 0.74, 95% confidence interval [CI]: 0.63–0.87; $P = .001$), lower average wound area (standard mean difference = –0.80, 95% CI: –1.54 to –0.06; $P = .034$), more wound area decrease (standard mean difference = 0.81, 95% CI: 0.36–1.26; $P = .001$), increased appearance rate of granulation tissue (RR = 1.61, 95% CI: 1.07–2.41; P-0.021), and lower risk of amputation or resection (RR = 0.70, 95% CI: 0.50–0.99; $P = .045$), were demonstrated for the NPWT group when compared to MWC group. However, no statistically significant difference was found for the disappearance rate of wound discharge at 8 weeks, the rate of blood culture positivity, VAS-pain score, and the overall frequency of adverse events between the 2 treatment groups ($P = .05$).

Conclusion: NPWT could accelerate process of the wound healing, and decrease the risk of post-treatment amputation or resection, without any additional frequency of adverse events, when compared with MWC, in patients with DFUs.

Abbreviations: CI = confidence interval, DFU = diabetic foot ulcer, IL = interleukin, MWC = moist wound care, NPWT = negative pressure wound therapy, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis, RCT = randomized controlled trial, RR = risk ratio, SMD = standard mean difference.

Keywords: diabetic foot ulcer, meta-analysis, moist wound care, negative pressure wound therapy

1. Introduction

Diabetes mellitus is one of the most common metabolic disease with high prevalence, having caused the heavy medical burden.[1,2] As reported by the International Diabetes Federation, there were 366 million diabetics in 2011, and by 2030 it was estimated that there would be 522 million patients with diabetes.[3] As a disabling complication of diabetes, diabetic foot ulcers (DFUs) are characterized with difficult-healing chronic wounds and treatment difficulties, rendering a severe challenge for clinical management.[4,5] Reportedly, diabetics had a 15% to 25% chance to develop DFU, and even after effective treatment, there was still a risk of recurrence rate of 50% to 70% for the ensuing 5 years,[6] ultimately leading to the amputations.

Various treatment strategies have been proposed to improve clinical outcomes for DFUs, including the moist wound care (MWC) and the negative pressure wound therapy (NPWT). Nevertheless, the optimal treatment choice for this disease is still undefined. As a novel, non-invasive treatment method, NPWT provides localized negative subatmospheric pressure via vacuum-assisted closure device to accelerate wound healing

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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with the mechanism of removing chronic interstitial wound fluid through a specified pump and improving tissue perfusion.[7–9] And increasing evidence has shown that this technique is effective in the clinical practice. Moreover, some studies further elaborated the underlying molecular mechanisms via basic experiments.[10–12] For example, Wang et al[11] recently discovered NPWT's anti-inflammatory effect through down-regulating MAPK-JNK signaling pathway in DFUs.

In recent years, some randomized controlled trials (RCTs) have been also conducted to evaluate the clinical efficacy of NPWT compared with MWC, and most of the studies achieved positive results. However, to our knowledge, there are no previous meta-analyses performed on this issue. Due to the existing controversy, therefore, we collected all available raw data from relevant RCTs to comprehensively compare the effectiveness and safety of the NPWT with the MWC, with the aim of providing a more reliable evidence for clinical application of NPWT.

2. Materials and Methods

2.1. Data retrieval

This study was performed according to guidelines outlined in Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.

Two reviewers independently searched the electronic platforms of the PubMed, EMBASE, and CENTRAL. Key words used for study retrieving include "Diabetic Foot," "Negative-Pressure Wound Therapies," "Vacuum-Assisted Closure," and so on. The detailed searching strategies are available in Table 1, Supplemental Digital Content, http://links.lww.com/MD/G885. In addition, the reference lists of the included studies were checked for identifying potential eligible studies.

2.2. Inclusion and exclusion criteria

Studies would be assessed for the eligibility for inclusion by 2 individual authors, according to the following inclusion criteria: (1) Participants: patients diagnosed with DFUs; (2) Intervention: the wound was treated with NPWT; (3) Comparison: the wound was treated with MWC; (4) Outcome: studies assessed the wound-related clinical outcomes; (5) Study: RCTs were included exclusively.

Studies would be excluded from the final inclusion, according to the exclusive criteria: (1) studies published with languages other than English; (2) duplicated studies; (3) non-RCTs.

2.3. Data extraction

After study retrieving on databases, the records were exported and checked for duplicates. The remained titles/abstracts were screened initially for potential eligibility after removing of the duplicates. Then, full-texts of the remained records were further assessed to identify the final eligible studies for qualitative and quantitative syntheses.

The related data were extracted by 2 authors independently, including the following items: (1) study information: lead author's name, publication year, study period, and country of first author; (2) patients characteristics: number of patients, male percentage, average age, drop-out patients, ulcer classification, and duration of ulcer; (3) treatment information: initial therapy before NPWT and MWC, device selected for application of negative pressure, and detailed protocols for NPWT and MWC; (4) clinical outcomes: wound status following treatment (wound closure rate, wound surface area, wound discharge, and appearance of granulation tissue), VAS-pain score, blood culture positivity, risk of amputation or resection, and the overall risk of adverse event. All of the above data were extracted by 2 authors independently, and all disagreements on the extracted data were solved by the third senior author.

2.4. Risk of bias assessment

The risk of bias of each included RCT was assessed utilizing the Cochrane Collaboration tool for assessing risk of bias.[13] This tool evaluated the risks of bias about the randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

2.5. Statistical analysis

The risk ratio (RR) and 95% confidence interval (95% CI) were selected as the effect size for dichotomous variables, while standard mean difference (SMD) and 95% CI was selected for continuous data. Quantitative pooling of the primary data was performed using fixed- or random-effect model according to the heterogeneity between studies. I^2 was used to detect the between-study heterogeneity, and I^2 value of more than 50% indicates significant heterogeneity, and random-effect model would be applied.

When more than 3 trials were included in a meta-analysis with significant heterogeneity, sensitivity analysis would be performed by omitting each primary study, to assess the stability of pooling result and identify the studies causing non-stability. Egger and Begg tests were performed to test the risk of publication bias when more than 5 studies were enrolled for analysis ($P = .1$ and $P = .05$ indicate significant publication bias for Egger and Begg tests, respectively).[14]

The "meta" package of *R* language ((*R* Foundation for Statistical Computing, Vienna, Austria) was used for statistical. *P* value of <.05 was regarded as statistically significant.

2.6. Ethics and dissemination

Ethical approval was not essential as all included data were obtained from published articles.

2.7. Patient and public involvement

This meta-analysis was performed by previously published data, thus no patient and public content was included in this study.

3. Results

3.1. Study searching and screening process

The initial retrieving in the electronic platforms identified a total of 977 records. Two records were additionally identified through searching by hand. After removing of 235 duplicated studies, 744 titles/abstracts were further screened for eligibility. Then, 63 remained full-text articles were assessed for final inclusion. As a result, 10 RCTs[8,9,15–22]were enrolled in qualitative synthesis and 8 RCTs[8,9,15–19] were enrolled for quantitative meta-analysis. The flow chart of study retrieving and selecting is available in Figure 1.

3.2. Characteristics of the primary RCTs

All of the included studies were 2-arm RCT. A total of 1244 patients were enrolled in the 10 primary RCTs, including 619 treated with NPWT and 625 treated with MWC. The male percentages in these treatment arms were ranges from 35.7% to 86.7%. The average age was ranged from 52.9 to 68.1 years old. In total, 58 patients were lost to the final follow-up in the 10 primary studies. The ulcer classification was available in 4 studies. Duration of ulcer at diabetic foot was

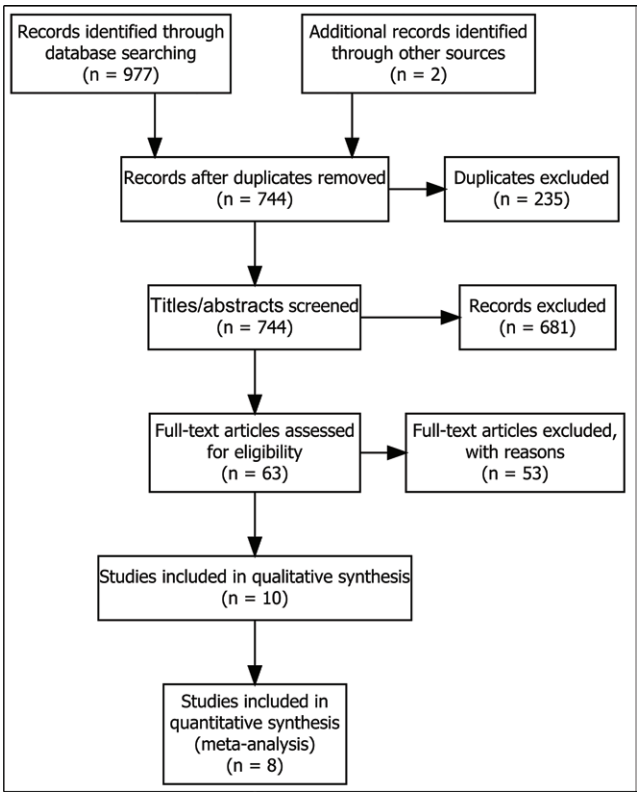

Figure 1. Flow chart of the study retrieval and selecting.

available in 4 studies, with an average duration between 3.1 and 7.2 months. The detailed summary of the included studies is shown in Table 1. Table 2 shows the treatment protocols for the included studies. Generally, the initial treatments mainly include debridement, antibiotics, and glycemic control. The type of negative pressure device was available in 5 studies. The negative pressures for NPWT were predominately set at −125 mm Hg in 5 RCTs, with intermittent or continuous modes. Different moist wound dressings were applied and changed daily or twice daily. Figure 2 presents the result of risk of bias assessment, showing no obviously high risk of bias existed for these 10 trials.

3.3. Wound-related outcomes

The overall wound closure rate was reported in 5 studies, with significant heterogeneity among these primary studies. A sensitivity analysis was performed to detect the studies causing non-stability, showing that the study of Seidel et al[15] caused significant non-stability (Figure 1, Supplemental Digital Content, http://links.lww.com/MD/G885). After omitting of this study, a new meta-analysis was conducted, and the result is shown in Figure 3. As a result, a significantly lower risk of non-closure of the wound was demonstrated for the NPWT group when compared to MWC group (RR = 0.74, 95% CI: 0.63–0.87; P = .001).

Figure 4 shows the results for comparison on wound area (A) and the wound area decrease (B). As a result, the NPWT group was found to be with significantly lower wound area (SMD = −0.80, 95% CI: −1.54 to −0.06, P = .034) and more wound area decrease (SMD = 0.81, 95% CI: 0.36–1.26, P = .001) when compared to that of the WMC group.

Figure 5 presents the forest plots for appearance of granulation tissue at 2 weeks (A) and disappearance of wound discharge at 8 weeks (B). It was demonstrated that the appearance rate of granulation tissue at NPWT group was higher than MWC group at 2 weeks following treatment (RR = 1.61, 95% CI: 1.07–2.41, P = .021). However, the disappearance rate of wound discharge was similar between 2 treatment groups at 8 weeks after therapy (RR = 1.08, 95% CI: 0.92–1.27; P = .331).

3.4. Blood culture positivity

The rates of blood culture positivity were reported in 3 primary trials, and the pooling result is shown in Figure 6, demonstrating that the NPWT was associated with non-significantly lower incidence of blood culture positivity than MWC group (RR = 0.73, 95% CI: 0.53–1.02, P = .062).

3.5. VAS-pain score

The VAS-pain score was available in 2 of the primary trials (Fig. 7). The pooling result showed that no difference on the VAS score at final follow-up was found between 2 treatment groups (SMD = −0.37, 95% CI: −1.28 to 0.54; P = .427).

3.6. Risk of amputation or resection

Figure 8 presents the forest plot for the risk of amputation or resection. A total of 5 primary trials were involved, with a fixed effect model. As a result, significantly lower risk of amputation or resection after treatment was found for the NPWT group than that of the MWC group (RR = 0.70, 95% CI: 0.50–0.99; P = .045). No significant publication bias was found according to Egger (P = .162) and Begg (P = .327) tests.

3.7. Adverse events

Two studies reported the overall frequency of adverse events, and the pooling result is available in Figure 9. It was found that the 2 treatment methods were associated with similar incidence of overall adverse events (RR = 1.10, 95% CI: 0.67–1.80; P = .720).

4. Discussion

DFU is the most frequent and intractable complication of diabetes, as well as the major cause of hospitalization, determining the prognosis of these patients to some extent. Although many treatment strategies have been developed for the clinical management of these patients, the outcomes of patients with DFUs are still frustrating. As a new emerging, non-invasive treatment system, NPWT has been advocated for its ability in manipulating the chronic wound environment to reduce bacterial burden and wound exudates, and increase vascularity and cytokine expression, thereby contributing to wound healing.[23] While, the MWC in patients with DFUs has been recognized as a standard wound care process. In this study, we obtained all available raw data from relevant RCTs and conducted a meta-analysis, demonstrating that NPWT is superior to MWC concerning the wound healing, and the risk of post-treatment amputation or resection, without increased risk of intolerance.

In the RCT of Wang et al,[11] they investigated the mechanism of regulation of mitogen-activated protein kinase-c-Jun N-terminal kinase signaling pathway by NPWT on diabetic foot wounds, demonstrating that NPWT could effectively alleviate inflammatory reaction and reduce interleukin (IL)-6 and inducible nitric oxide synthase production at 7 days following treatment, and decrease the level of tumor necrosis factor-a, IL-6 and P-c-Jun N-terminal kinase. Karam et al[10] also researched the molecular mechanism of NPWT in DFUs, finding that after 10 days of treatment with NPWT, levels of IL-1β, tumor necrosis factor-a, matrix metalloproteinase-1, and matrix metalloproteinase-9 were significantly down-regulated, while levels of vascular endothelial growth factor,

Table 1

Summary of the included studies.

Author	Year	Study period	Country	Study groups	Patients number	Male%	Average age	Drop out	Ulcer classification	Duration of ulcer
Seidel et al[15]	2020	December 2011–August 014	Germany	NPWT	181	77.8	67.6 ± 12.3	10	Primary: 136 (79.5%); recurrence: 34 (19.9%)	Mean: 217.1 ± 458.1 d
				MWC	187	77.0	68.1 ± 11.5	13	Primary: 143 (82.2%); recurrence: 29 (16.7%)	Mean: 162.1 ± 220 d
James et al[16]	2019	NA	India	NPWT	30	59.3	55.9 (35–95)	3	Wagner grade 1: 8 (29.63%); Wagner grade 2: 19 (70.37%)	NA
				MWC	30	55.6	52.9 (28–70)	3	Wagner grade 1: 2 (7.41%); Wagner grade 2: 25 (92.59%)	
Sajid et al[17]	2015	November 2010–June 2012	Pakistan	NPWT	139	77.0	56.8 ± 11.3	0	Wagner grade 1: 17 (12.2%); Wagner grade 2: 122 (87.8%)	NA
				MWC	139	82.0	55.9 ± 11.0	0	Wagner grade 1: 25 (18%); Wagner grade 2: 114 (82%)	
Lone et al[9]	2014	NA	India	NPWT	28	35.7	53.8 ± 4.5	0	NA	NA
				MWC	28	35.7	54.6 ± 4.8	0		
Ravari et al[8]	2013	NA	Iran	NPWT	10	70.0	NA	0	Wagner grade 2: 1 (11.1%) Wagner grade 3: 2 (22.2%); Wagner grade 4: 6 (66.7%)	Mean: 6.1 ± 10.7 mo
				MWC	13	61.5		0	Wagner grade 1: 1 (7.7%); Wagner grade 3: 7 (53.8%); Wagner grade 4: 5 (38.5%)	Mean: 3.1 ± 1.7 mo
Nain et al[18]	2011	NA	India	NPWT	15	80.0	61.33 ± 7.6	0	NA	NA
				MWC	15	86.7	55.40 ± 11.5	0		
Blume et al[19]	2008	August 2002–August 2005	United States	NPWT	172	83.0	58.0 ± 12.0	1	NA	Mean: 198.3 ± 323.5 d
				MWC	169	73.0	59.0 ± 12.0	5		Mean: 206.0 ± 365.9 d
Etoz[21]	2007	NA	NA	NPWT	12		66.2 (54–77)	10	NA	NA
				MWC	12		64.7 (56–74)	13		
Eginton et al[20]	2003	NA	United States	NPWT	5	NA	NA	0	NA	NA
				MWC	5			0		
Riaz et al[22]	2010	March 2009–September 2009	Pakistan	NPWT	27	70.0	54.0 ± 6.3	0	NA	3–4 mo: 23; 4–5 mo: 4
				MWC	27	70.0	53.0 ± 5.3	0		3–4 mo: 23; 4–5 mo: 4

MWC = moist wound care, NA = not available, NPWT = negative pressure wound therapy.

Table 2

Treatment protocol in each included study.

Study ID	Initial therapy	Negative pressure device	Protocol for negative pressure therapy	Protocol for moist wound care
Seidel et al[15]	Amputation, debridement, or thorough wound cleansing	CE-marked NPWT devices of the manufacturers Kinetic Concepts Incorporated (KCI) and Smith & Nephew(S&N)	Intermittent and continuous NPWT was used with negative pressure to be adapted as recommended for the dressing applied and adapted to the wound needs	NA
James et al[16]	Debridement of the wound, antibiotics and glycemic control	A wall-mounted suction device	Pressure was set at −125 mm Hg; mode of NPWT was continuous	Saline-soaked gauze piece; changed daily
Sajid et al[17]	Debridement	Medela® Dominant 50 high vacuum suction	Pressure was set at −125 mm Hg; mode of NPWT was intermittent	Moist dressings; changed daily
Lone et al[9]	Sharp surgical debridement, and remove necrotic tissue and slough	NA	Pressure was set at −80 to −125 mm Hg; mode of NPWT was intermittent	Saline-soaked gauzedressing; changed daily
Ravari et al[8]	NA	Manufactured by KCI Medical Ltd., England	Controlled negative pressure up to 125 mm Hg	Moist bandage; changed twice daily after washing the ulcer with sterile serum
Nain et al[18]	Sharp debridement to remove necrotic tissue and slough	NA	Pressure was set at −80 to −125 mm Hg; mode of NPWT was intermittent	Saline-moistened gauze; changed twice daily
Blume et al[19]	NA	NA	Pressure was set at −50 to −200 mm Hg; mode of NPWT was continuous	MWT dressings were used according to Wound, Ostomy and Continence Nurses Society guidelines and institutional treatment protocols
Etoz[21]	Surgically debrided of nonviable tissue	NA	Pressure was set at −125 mm Hg; mode of NPWT was continuous	Traditional moist gauze dressings; changed twice daily
Eginton et al[20]	Sharp debridement	The vacuum-assisted closure device	Pressure was set at −125 mm Hg; mode of NPWT was continuous	Hydrocolloid wound gel and gauze dressings; changed daily
Riaz et al[22]	NA	NA	NA	Changed according to dressing soakage and discharge from the wound

NA = not available, NPWT = negative pressure wound therapy, MWC = moist wound care.

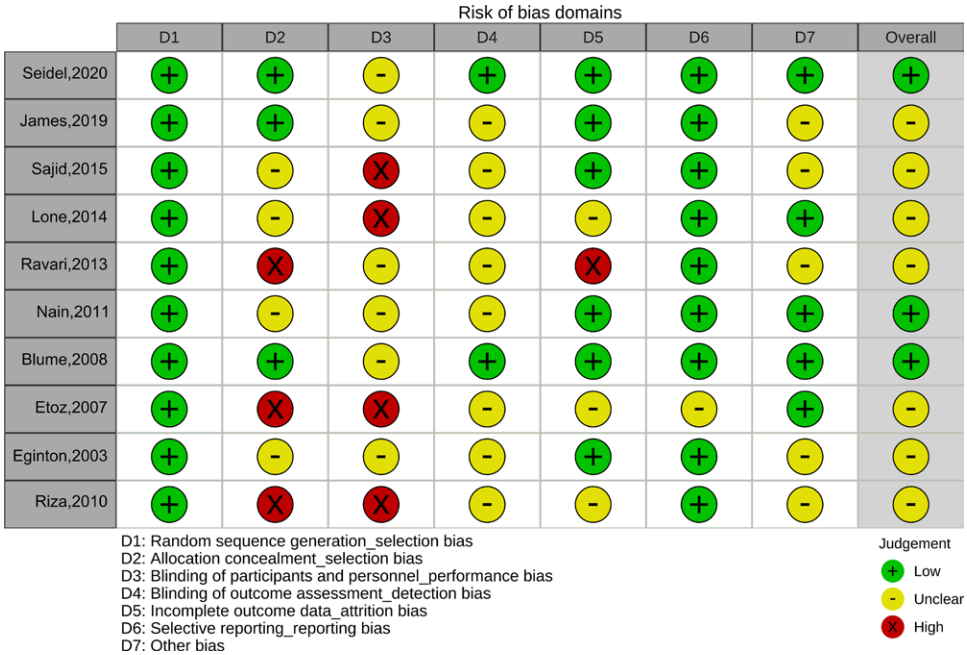

Figure 2. Result of risk of bias assessment using the Cochrane Collaboration tool.

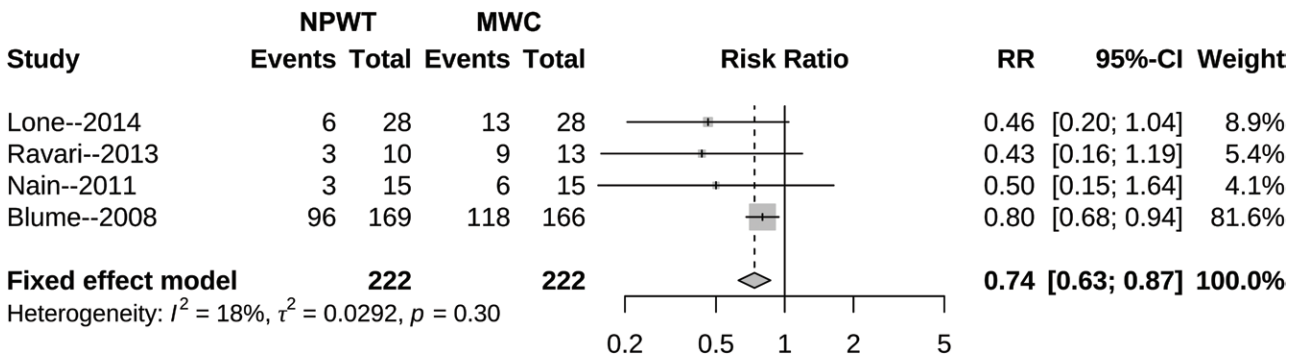

Figure 3. Forest plot for the comparison of wound closure rate between NPWT and MWC groups. CI = confidence interval, MWC = moist wound care, NPWT = negative pressure therapy, RR = risk ratio.

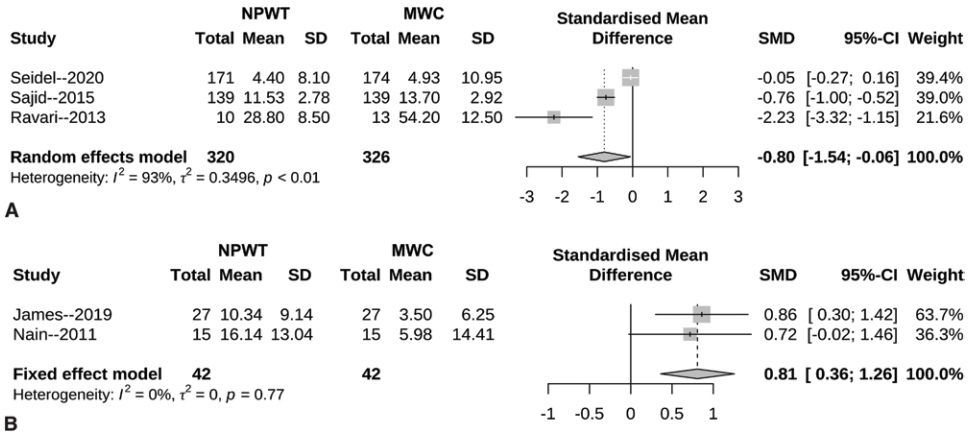

Figure 4. Forest plot for the comparisons of wound area (A) and wound area decrease (B) between NPWT and MWC groups. CI = confidence interval, MWC = moist wound care, NPWT = negative pressure therapy, SD = standard deviation, SMD = standard mean difference.

TGF-β1 and tissue inhibitor metalloproteinase-1 were significantly increased, when comparing to that of the patients treated with MWC. Yang et al[6] also showed that NPWT facilitated the production of cellular fibronectin and the expression of TGF-β1 in granulation tissue in DFUs compared to that of the MWC treatment. Thus, through many complex molecular pathways, the NPWT could provide the patients with an accelerated healing on the wounds.

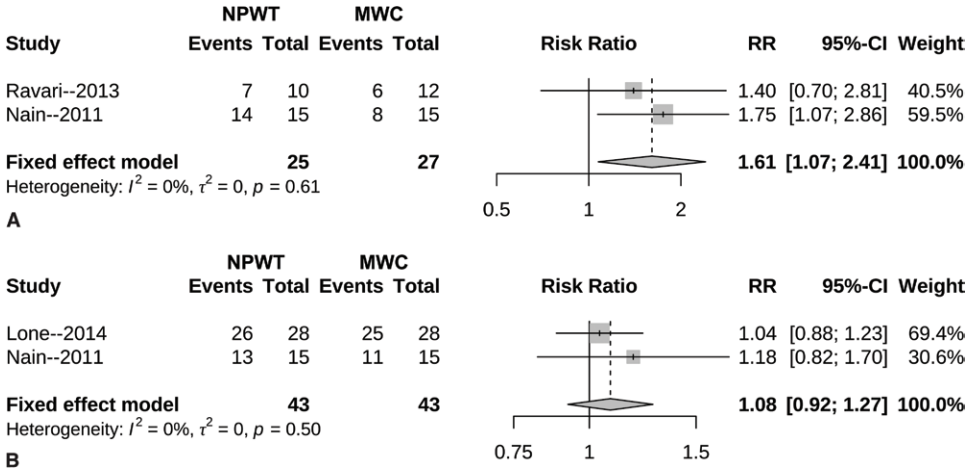

Figure 5. Forest plot for the comparisons of appearance rate of granulation tissue at 2 wk (A) and disappearance rate of wound discharge at 8 wk (B) between NPWT and MWC groups. CI = confidence interval, MWC = moist wound care, NPWT = negative pressure therapy, RR = risk ratio.

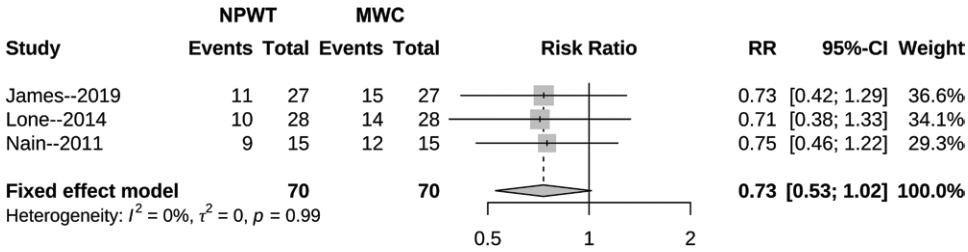

Figure 6. Forest plot for the comparison of incidence of blood culture positivity between NPWT and MWC groups. CI = confidence interval, MWC = moist wound care, NPWT = negative pressure therapy, RR = risk ratio.

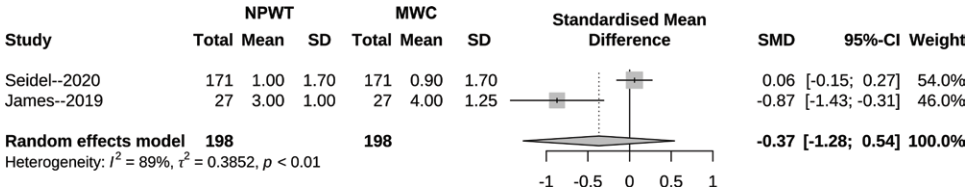

Figure 7. Forest plot for the comparison of VAS-pain score between NPWT and MWC groups. CI = confidence interval, MWC = moist wound care, NPWT = negative pressure therapy, SD = standard deviation, SMD = standard mean difference.

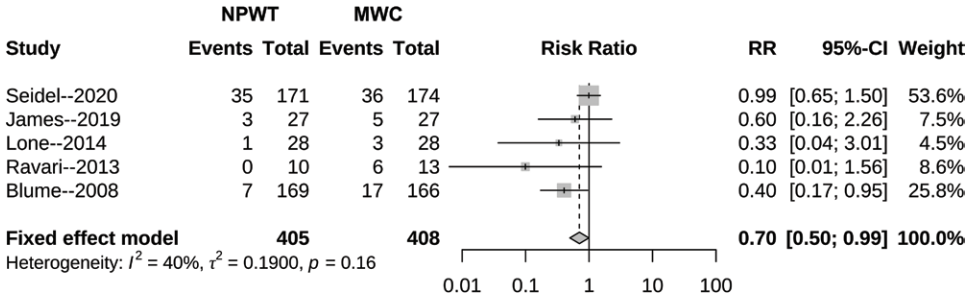

Figure 8. Forest plot for the comparison of risk of amputation or resection after treatment between NPWT and MWC groups. CI = confidence interval, MWC = moist wound care, NPWT = negative pressure therapy, RR = risk ratio.

Recently, Seidel et al[15] conducted a RCT to compare the clinical outcome of patients treated with NPWT and MWC for DFUs. As a result, neither the wound closure rate nor the time to wound closure was significantly different between the treatment arms. However, most of the other studies showed that the NPWT was significantly more efficacious than MWC in DFU patients. Lone et al[9] compared the effectiveness of NPWT versus MWC in the healing of DFUs. They found that granulation tissue appeared in 92.85% and 53.57% of the patients at 2 weeks in NPWT and MWC groups, respectively. Full granulation was achieved in 77.78% and only 40.00% patients at 5 weeks in NPWT and MWC groups, respectively. Patients in NPWT group had significantly fewer number of positive blood cultures, secondary amputations and were more satisfied with

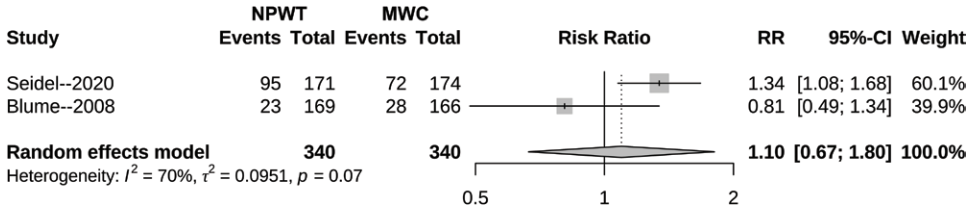

Figure 9. Forest plot for the comparison of overall frequency of adverse event between NPWT and MWC groups. CI = confidence interval, MWC = moist wound care, NPWT = negative pressure therapy, RR = risk ratio.

treatment as compared to MWC group. Hence, they concluded that NPWT was associated with increased effectiveness, safety, and patient satisfactory, compared to MWC group. Riaz et al[22] also reported that appearance of granulation tissue was more rapid in NPWT group as compared to MWC group (mean: 17.5 vs 37.5 days). Our results were in accordant with these studies, showing superior efficacy of NPWT in patients with DFUs.

The current study also demonstrated that no additional risk of adverse events was associated with NPWT application when compared to MWC. In addition, by applying of negative pressure device, the incidence of post-treatment amputation or resection could be decreased.

This study, however, has some limitations that must be acknowledged. First, in spite of the randomized controlled design, the quality of some included studies was relatively low owing to their undisclosed details of study methods, like the randomization, concealment, and blinding methods, which may lead to bias. Second, some RCTs had relatively small sample size making their results somewhat unreliable. Finally, data for some outcomes were only available in a few primary studies, causing the small number of patients involved in the meta-analyses. Thus, some more high-quality RCTs are necessary to further identify the treatment effectiveness of NPWT versus MWC.

5. Conclusions

Based on the available RCTs, this study found that NPWT could accelerate process of the wound healing, and decrease the risk of post-treatment amputation or resection, without increased frequency of adverse events, when compared with MWC, in patients with DFUs.

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